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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/466,035 12/17/99 SALLBERG

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SEED INTELLECTUAL PROPERTY LAW GROUP PLL
701 FIFTH AVE
SUITE 6300
SEATTLE WA 98104-7092

EXAMINER

PARAS JR, P

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

02/02/01

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/466,035

Applicant(s)

SALLBERG ET AL.

Examiner

Peter Paras

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 December 2000.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 12 and 13 is/are pending in the application.
- 4a) Of the above claim(s) 6-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 12-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group 1, claims 1-13, in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' response to the restriction requirement includes the election of a species of intracellular pathogen, particularly virus, and more particularly HIV. Additionally Applicants response to the restriction requirement includes the election of a species of vector construct, particularly nucleic acid vectors that are alphaviruses. Thus, given the elected species, claims 1-5, and 12-13 are examined below. Claims 6-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' claimed invention is drawn to methods of treating an intracellular infection within a warm-blooded animal comprising a) administering to a warm-blooded animal a vector construct which directs the expression of at least one immunogenic portion of an antigen derived from an intracellular pathogen; and b) administering to said warm-blooded animal a protein which comprises said immunogenic portion of said antigen, such that an immune response is generated. It is initially noted that applicant specification fails to define treatment. Furthermore, the claims as written do not provide a positive process step that relates back to the preamble of the claim, such that treatment is defined within the claims as written. When the claims are read in light of the specification, it is clear that the term "treatment" is intended to have a therapeutic connotation (see page 3 of the specification, 2nd full paragraph, for example). The claims have been interpreted in this manner for the purposes of examination under 35 USC § 112, first paragraph since the only apparent use for *in vivo* delivery is therapeutic treatment. It is further noted that the term "intracellular pathogen" has been interpreted as only encompassing the treatment of intracellular bacteria, parasitic and viral infections, as specified on page 3 of the specification lines 20-21. Furthermore, based on the species election to viruses, the term "intracellular pathogen" is examined only as it pertains to viruses, particularly HIV, hereinafter.

At the time of the claimed invention, gene therapy was well established as an unpredictable art. This is supported by the teachings of Marshall, and Verma et al.

Marshall et al states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cell-and getting them expressed-remain a nagging problem for the entire field" (page 1054, column 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "[t]he actual vectors-how we're going to practice our trade-haven't been discovered yet" (page 1055, column 2).

Verma et al (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to these problems had not been achieved in the art (see entire article). Verma et al further emphasizes, that despite improvements in vector technology, the actual vectors for which gene therapy can be practiced need to be streamlined further to assure effective and efficient vector targeting and desired immune reactions (see page 242, for example).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation (as evidenced by the references cited above). These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its

secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. While applicant's specification provides guidance to constructing various vectors and provides some *in vitro* indicators that an immune response is generated following the administration of 1) a vector encoding an immunogenic antigen (that of hepatitis B core antigen) and 2) recombinant HbcAG (see example 16), the specification fails to provide any evidence of therapeutic benefit as a result of generating this specific immune response. In other words, there is no evidence in the unpredictable gene therapy art that the immune response generated reaches therapeutic threshold levels *in vivo*; there is no evidence that the *in vitro* parameters measured are correlative to any therapeutic benefit. Finally, with regard to the elected species of HIV (intracellular pathogen) and alphavirus (vector), the specification fails to provide guidance, relevant teachings, or working examples to enable the skilled artisan to construct and use an alphavirus vector comprising a nucleic acid molecule that encodes an HIV peptide, for treatment of HIV.

At the time of the claimed invention, the field of alphavirus vectors was an unpredictable art. This is supported by the teachings of Frolov, Ohno, and Garoff et al.

Frolov et al teach that in permissive cells, virus infection results in the rapid shut off of host mRNA translation, takeover of the translational machinery by viral mRNAs, production of high titers of infectious virus, and cell death within 12-24 hours. See page 11374, top of column 2. Frolov et al further teach that for applications requiring long-term expression and minimal perturbation of vertebrate host cell biology, alphavirus-induced shut-off of host mRNA translation and cell death are undesirable. With regard

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to tissue specificity Frolov et al teach that alphaviruses replicate in a variety of tissues but that there are substantial differences in tissue tropism for a particular alphavirus or among alphaviruses. Frolov et al also teach that little is known about the viral determinants, cognate cell surface receptors, and intracellular environments that modulate entry and replication. See page 11374 column 2.

Ohno et al teach that a major drawback to the use of Sindbis virus, an alphavirus, is that "these vectors lack target-cell specificity". See page 763. Ohno et al also teach that Sindbis virus infection of vertebrate cells usually results in cell death by apoptosis and that recombinant Sindbis virus vector developed in this study still has low infectivities. See page 766.

Garoff et al teach that there have been two major challenges for further development of the alphavirus vectors. One is to decrease the cytopathogenicity of these vectors, a feature which in practice makes only transient gene expression feasible with these systems. Another is to restrict infection of alphavirus vectors to a predetermined target cells. Garoff et al teach that the use of alphavirus vectors is associated with cytopathic effects and host cell death within 1-2 days; this has limited the usefulness of this vector system for the purposes of protein production and gene therapy. See page 766, column 2. Garoff further teach that alphavirus vectors have a very wide host range that allows gene expression possible in many different types of cell cultures. "However, the wide host range is problematic if the vectors are used in gene therapy. In this case, gene expression usually needs to be restricted to certain cell types."

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for in vivo therapeutic benefit, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to in vivo cell transformation and gene therapy, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete. The claim as written does not provide a positive process step that relates back to the preamble of the claim, such that treatment is defined within the claims as written. Furthermore, applicants' specification fails to define treatment such that the metes and bounds of the concept of treatment can be discerned. Additionally, in claim 1, step (a), the term derived is indefinite. Derived tends to imply a lineage of development, however, this does not appear to be the context for which applicants are using the term. It is suggested that the term "isolated" be used instead of "derived" to clarify the claim.

Claim 1 is further indefinite, because it is unclear whether the immunogenic portion of an antigen administered in step (b) need to be the same immunogenic portion of antigen administered in step (a), or just one of a variety of immunogenic portions administered in step (a). In other words, step (a) recites the administration of "at least one immunogenic portion of an antigen", step (b) recites the administration of said immunogenic portion of step (a), however, step (a) can comprise numerous immunogenic portions. Thus, it is unclear if step (b) is the administration of all immunogenic portions of step (a) or whether it can be just one immunogenic portion. Clarification is necessary. Claims 2-5 and 11-12 depend from claim 1.

Claim 5 is indefinite because the phrase "said viral antigen" lacks antecedent basis in claim 3 from which it depends. It appears claim 5 is intended to depend from claim 4, rather than claim 3. Correction is necessary.

Conclusion

No claims are allowed. Claims 1-5 and 12-13 are free of the prior art of record because the prior art of record does not teach or suggest a method of treatment comprising administration to a warm-blooded animal an alphavirus construct that directs the expression of an immunogenic portion of an HIV antigen and a protein which comprises the same immunogenic portion of an HIV antigen. The claims, however, are subject to other rejections.

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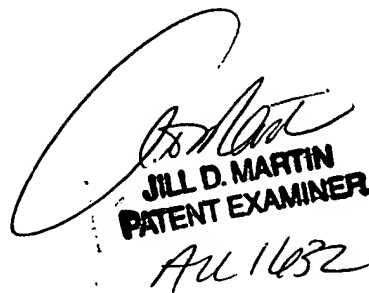
Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinckney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

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JILL D. MARTIN
PATENT EXAMINER
AU 1632